Non-Feasibility to Estimate the Need for Reversal of Neuromuscular Relaxation from the Applied Rocuronium Dosing Pattern: A Retrospective Analysis of Anaesthesia Records

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Abstract: Objective: Some anaesthetists are convinced that a long interval since the last relaxant dose may be sufficient to recover from anaesthesia without a pharmacological reversal. We intended to demonstrate that the dosing pattern of rocuronium could not predict the necessity of reversal. Methods: In a cohort analysis, we retrospectively analysed 180 anaesthesia records of adult patients who underwent elective surgical interventions in general anaesthesia and tracheal intubation with rocuronium-induced neuromuscular blockade. The extracted records were divided to 3 post hoc groups of 60 each, according to the reversal method employed at the end of anaesthesia: group N with neostigmine, group S with sugammadex and group Z without pharmacological reversal. All cases were terminated after achieving a train of four ratio of 0.9. Dosing patterns of rocuronium were compared by applying a novel pharmacometric calculation method, residual drug activity coefficient (RDAC), which employs both the administered individual drug doses in mg kg-1 and the timing of each drug administration in relation to the time of extubation. The rocuronium dosing pattern was correlated with the employed method of neuromuscular blockade reversal. Results: The dosing for rocuronium in patients without pharmacological reversal was lower than that in both reversal agent groups (n=0.58±0.21, S=0.58±0.17 and Z=0.47±0.17), but there was still a large overlap in the RDAC. Conclusion: The dosage profile of rocuronium alone cannot predict the possibility to refrain from pharmacological reversal.

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Uygulanan Rokuronyum Dozaj Şeklinden Nöromüsküler Bloğu Geri Döndürme Gereksiniminin Tahmin Edilememesi: Anestezi Kayıtlarının Retrospektif Bir Analizi

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Abstract / Öz

Objective: Some anaesthetists are convinced that a long interval since the last relaxant dose may be sufficient to recover from anaesthesia without a pharmacological reversal. We intended to demonstrate that the dosing pattern of rocuronium could not predict the necessity of reversal.

Methods: In a cohort analysis, we retrospectively analysed 180 anaesthesia records of adult patients who underwent elective surgical interventions in general anaesthesia and tracheal intubation with rocuronium-induced neuromuscular blockade. The extracted records were divided to 3 post hoc groups of 60 each, according to the reversal method employed at the end of anaesthesia: group N with neostigmine, group S with sugammadex and group Z without pharmacological reversal. All cases were terminated after achieving a train of four ratio of 0.9. Dosing patterns of rocuronium were compared by applying a novel pharmacometric calculation method, residual drug activity coefficient (RDAC), which employs both the administered individual drug doses in mg kg^{-1} and the timing of each drug administration in relation to the time of extubation. The rocuronium dosing pattern was correlated with the employed method of neuromuscular blockade reversal.

Results: The dosing for rocuronium in patients without pharmacological reversal was lower than that in both reversal agent groups (n=0.58±0.21, S=0.58±0.17 and Z=0.47±0.17), but there was still a large overlap in the RDAC.

Conclusion: The dosage profile of rocuronium alone cannot predict the possibility to refrain from pharmacological reversal.

Keywords: Neuromuscular blockade, extubation, rocuronium, reversal

Amaç: Bazı anestezi uzmanlarına göre, en son uygulanan nöromüsküler bloker dozundan itibaren geçen uzun bir aralık, farmakolojik bir geri dönüş olmaksızın, anesteziden sonra derlenme için yeterlidir. Bu çalışmada amaç rokurunyum dozaj şeklinin, geri dönüş gerekliliğini öngöremediğini göstermektir.

Yöntemler: Bu kohort çalışmada, genel anestezi altında elektif cerrahi müdahale ve rokuronyum ile indüklenen nöromusküler blokaj ile trakeal intübasyon uygulanan 180 yetişkin hastanın anestezi kayıtları retrospektif olarak değerlendirildi. Elde edilen kayıtlar, anestezi sonunda uygulanan geri dönüş yöntemine göre her biri 60 kişiden oluşan 3 post hoc gruba ayrıldı: neostigmin kullanılan Grup N, sugammadeks kullanılan Grup S ve farmakolojik geri dönüş kullanılmayan Grup Z. Tüm vakalar "train of four" oranı 0.9 elde edilince sonlandırıldı. Rokuronyumun doz paterni, yeni bir farmakometrik hesaplama metodu (rezidüel ilaç aktivite katsayısı) uygulanarak karşılaştırıldı. Bu katsayı mg kg^{-1} olarak uygulanan bireysel ilaç dozlarını ve ekstübasyon zamanıyla ilişkili olarak her ilaç uygulama zamanlamasını kullanmaktadır. Rokuronyum dozaj şekli ile uygulanan nöromusküler blokaj geri dönüş yöntemi ile ilişkiliydi.

Bulgular: Farmakolojik geri dönüş kullanılmayan hastalarda rokuronyum dozajı, geri dönüş ajanı kullanılan diğer iki gruba göre daha düşüktü (n=0,58±0,21, S=0,58±0,17 ve Z=0,47±0,17). Ancak RDAC değerinde halen büyük bir örtüşüm (overlap) vardı.

Sonuç: Tek başına rokuronyum dozaj profili farmakolojik geri dönüşten kaçınma olasılığını öngöremez.

Anahtar Kelimeler: Nöromusküler blokaj, ekstübasyon, rokuronyum, geri dönüş

Introduction

It is a widespread belief among anaesthesiologists that the spontaneous recovery of neuromuscular blocking agents (NMBA) may be sufficient to avoid postoperative residual paralysis (PORP), if enough time has passed since the last NMBA administration. In these cases, it is assumed that pharmacological reversal may not be necessary. However, the time course of spontaneous recovery is dependent on a multitude of factors; the duration for sufficient recovery of neuromuscular transmission is difficult to predict (1, 2). Understandably, the practice of relying only on the natural decay of

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NMBA cannot be substantiated by prospective investigations for ethical reasons. Instead, it is possible to retrospectively analyse rocuronium dosing patterns from electronically archived anaesthesia records with the aim to compare the dosing patterns of rocuronium and pharmacologic antagonists. All three different practices may be correct and acceptable, if, at the time of extubation, the neuromuscular transmission has recovered to a train of four (TOF) ratio of at least 0.9, which in turn must have been confirmed by quantitative relaxometry. In this investigation, we analysed anaesthetic records from cases in which rocuronium was antagonised with either neostigmine or sugammadex or in which rocuronium was allowed to recover spontaneously without reversal. The time to reversal was compared in the context of dosing patterns over time while having arrived at a neuromuscular function of a TOF ratio of 0.9 (3-6).

Methods

In a single-centre, retrospective study, we extracted data from archived electronic anaesthesia records in which rocuronium was used as the only NMBA for the entire surgical procedure, and at termination of anaesthesia, the TOF ratio has recovered to 0.9 either with or without a pharmacological reversal. The Cantonal Ethical Committee approved this investigation (No. 2016-01202, chaired by Peter Meier-Abt) necessitating that patient data should be de-identified to protect personal health information. Informed consent from the patients was not required. To obtain comparable groups with different reversal strategies for avoiding PORP and after performing a power analysis, we selected 180 of the most recent anaesthesia records that met our inclusion criteria and divided them to three post hoc study groups:

- Group N=reversal of rocuronium-induced neuromuscular block with neostigmine (n=60).
- Group S=reversal of rocuronium-induced neuromuscular block with sugammadex (n=60).
- Group Z=spontaneous recovery of rocuronium without pharmacological reversal (n=60).

The investigated parameter was the underlying rocuronium dosage pattern expressed in a defined residual drug activity coefficient (RDAC) at end of anaesthesia (7). In a preliminary power analysis of the expected differences between the groups due to the duration of action variability of rocuronium, a sample size of 180 was considered sufficient.

The inclusion criteria were general anaesthesia with tracheal intubation and neuromuscular relaxation with rocuronium in patients undergoing elective surgery, with a duration of anaesthesia >60 minutes. Exclusion criteria were the use of other muscle relaxants and sedative drugs, such as dehydrobenzperidol or clonidine, (8) and with neuromuscular diseases or other conditions that may affect neuromuscular function.

All the cases were performed as total intravenous anaesthesia with propofol for induction and maintenance of anaesthesia and analgesia with fentanyl/remifentanil combinations. All patients were extubated at the end of surgery as per usual clinical routine, based on the anaesthetists' clinical judgement. The termination of anaesthesia was permitted as soon as the return of neuromuscular transmission has arrived at 0.9 TOF ratio either with or without pharmacological reversal.

Determination of the individual residual drug activity coefficient (RDAC)

To compare dosing patterns of rocuronium, we used the RDAC method, which is a pharmacometric calculation method (7) employing both the administered repetitive individual drug doses (mg kg^{-1}) and the timing of each drug administration in relation to a defined reference time. As reference time for the RDAC calculations we used the time of extubation. RDAC is an ideal tool to describe drug amount and time related dosage patterns. In particular, it considers the fact that drug doses given closer to the reference time have a stronger residual effect, which indicates a more pronounced residual neuromuscular weakness compared to an identical total dose per body weight and time that has been administered predominantly earlier during the same time frame.

The formula to calculate RDAC is as follows:

$$RDAC = \left(\frac{D1/m}{\Delta T1}\right) + \left(\frac{D2/m}{\Delta T2}\right) \ldots + \left(\frac{Dn/m}{\Delta Tn}\right)$$

where D/m is a particular bolus dose in mg/kg and ΔT is the time difference between drug application and reference time in minutes. The numerals indicate consecutive bolus doses with 1 representing the first bolus, 2 representing the second bolus, on and so forth.

Data acquisition and analysis

The extracted records were divided into the 3 post hoc study groups N, S and Z with 60 cases each. The following demographic and clinical data were collected from de-identified patient records:

- Patients' age, gender, weight and height.
- Duration of anaesthesia.
- Rocuronium dosage profile (according to RDAC) (Biro 2013).
- Choice of reversal agents and their dosage or non-reversal.

Statistical analysis

The power analysis was based on an ANOVA-test using three groups, an a-error probe of 0.05, a power of 90%, and an estimated effect size of 0.3, resulting in a total sample size of 180. The Chi-square test was used for analysis of nominal and ordinal data. For continuous data, normality was tested using the Shapiro-Wilk normality test. Normally distributed data were compared by one-way ANOVA, not normally distributed data using Kruskal–Wallis test and multiple comparisons were corrected using the Tukey's or Dunn's multiple comparison tests, respectively. A p value of <0.05 was considered statistically significant.

Power calculation was performed using G*Power 3.1 (G*Power, Düsseldorf, Germany) and statistical analyses were calculated using GraphPad Prism (GraphPad Incorp, San Diego, CA).

Results

The 180 analysed cases originated from March to September 2016 at the University Hospital Zurich. The assembled three post hoc groups of patient records from precedent anaesthetics were comparable with regard to biometric data of the involved patients (Table 1). A statistically significant difference was found in body weight, which however may be considered clinically irrelevant since the compared rocuronium doses were calculated on a mg kg^{-1} basis. There was also a slight difference in the anaesthesia duration between the neostigmine and sugammadex reversal groups (N vs. S) but not between these groups and the natural decay group (Z).

Neither the total individual doses of rocuronium nor the doses adjusted to body weight showed a significant difference in the 3 post hoc groups. However, when the timing context was included to describe the dosing pattern by comparing RDAC, a statistically significant difference to the natural decay group (Z) was found (Table 2), albeit there was a large overlap of rocuronium dosing in all three groups (Figure 1). The RDAC for rocuronium in Group Z was on an average lower than that in both the reversal agent groups (which

Table 1. Demographics and clinical data of the patients from the extracted anaesthesia records

n=180	Group N (n=60) Reversal with neostigmine	Group S (n=60) Reversal with sugammadex	Group Z (n=60) No reversal (natural decay)	Statistical significance
Gender distribution	25M/35F	31M/29F	31M/29F	N vs. S: n.s. N vs. Z: n.s. Z vs. S: n.s.
Age (years) mean±SD	56±18	61±15	50±17	N vs. S: n.s. N vs. Z: n.s. Z vs. S: n.s.
Height (cm) mean±SD	168±9	169±8	172±9	N vs. S: n.s. N vs. Z: n.s. Z vs. S: n.s.
Weight (kg) mean±SD	70±18	83±22	78±22	N vs. S< 0.05 N vs. Z: n.s. Z vs. S: n.s.
Duration of anaesthesia (min) mean±SD	217±96	203±71	224±80	N vs. S< 0.05 N vs. Z: n.s. Z vs. S: n.s.

n.s.: no statistically significant difference; M: male; F: female

Table 2. Rocuronium doses and dosing patterns

n=180	Group N (n=60) Reversal with neostigmine	Group S (n=60) Reversal with sugammadex	Group Z (n=60) No reversal (natural decay)	Statistical significance
Total individual rocuronium dose (mg) mean±SD	90±31	84±26	90±29	N vs. S: n.s. N vs. Z: n.s. Z vs. S: n.s.
Rocuronium dose per body weight (mg kg^{-1}) mean±SD	1.3±0.4	1.05±0.31	1.18±0.33	N vs. S<0.05 N vs. Z: n.s. Z vs. S<0.05
Rocuronium dose per body weight and anaesthesia duration (mg kg^{-1} h^{-1}) mean±SD	0.4±0.15	0.33±0.11	0.34±0.12	N vs. S: n.s. N vs. Z: n.s. Z vs. S: n.s.
Residual drug activity coefficient mean±SD	0.58±0.21	0.58±0.17	0.47±0.17	N vs. S: n.s. N vs. Z<0.05 Z vs. S<0.05

n.s.: no statistically significant difference

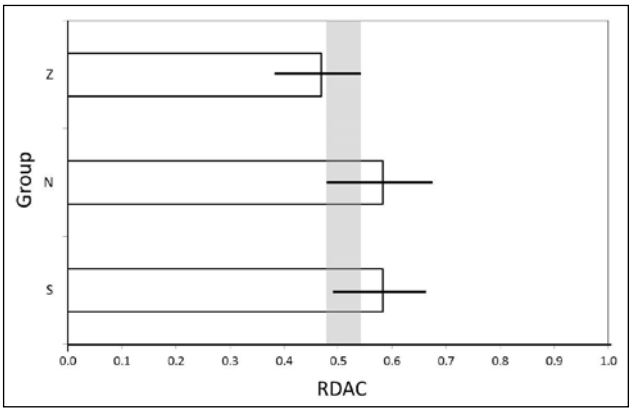

Figure 1. Residual drug activity coefficient in the three study groups (mean±SD). The grey zone indicates the overlap zone of 1 SD, which means that one cannot safely distinguish the necessity for reversal from the administered rocuronium dosage pattern

otherwise had the same RDAC). This indicates a tendency for the omission of pharmacological reversal if the rocuronium dosage profile was considered suitable for non-reversal by the involved anaesthetists, and a TOF ratio of 0.9 confirmed this circumstance.

Discussion

There are indications that PORP may be associated with postoperative morbidity and mortality and therefore must carefully be avoided (4-6, 9). Hence, there is a generally accepted consensus that neuromuscular transmission should return to normal before the end of anaesthesia which can be confirmed by a minimum TOF ratio of 0.9. This condition became a standard operating procedure in our department. This threshold can only be recognized by monitoring the neuromuscular function objectively throughout the procedure. In routine clinical practice, we often hear the opinion of colleagues that if "a long enough time" has passed since the last administration of rocuronium (or another non-depolarizing neuromuscular blocking agent (NMBA), a sufficient neuromuscular recovery can be expected. However, those advocating this reliance on the spontaneous recovery of the relaxant cannot establish a safe time lag or time-related dosing pattern that would be indicative of a safe recovery from anaesthesia. Such an attitude has been repeatedly questioned by authors who have shown the large variability of the action duration of NMBA in clinical practice (10). In patients without previous reversal of NMBA, a prevailing PORP may be present, although the anaesthetist erroneously might believe that his/her patient may be fit for unassisted spontaneous breathing via a safely protected airway. The tendency to adopt this practice might be reinforced by a clinician's desire to avoid the undesirable side effects of reversal with the cholinesterase-blocker neostigmine and by economic considerations related to sugammadex.

With our investigation, we intended to determine whether there is a difference in the dosing pattern of rocuronium in the actual routine practice of our colleagues, which might help distinguish if reversal was necessary or could be omitted. The hereby-applied RDAC is the most appropriate pharmacometric parameter because it not only considered the repetitive rocuronium doses per body weight and the total duration of rocuronium administration, but also particularly displays the dosing/time-relationship towards the reference time of extubation. The RDAC values extracted from our study revealed a lower mean RDAC for the natural decay group (Z) at 0.47 compared to 0.58 for both reversal groups, indicating that there was a tendency to omit pharmacological reversal in cases with a longer time duration since the relaxant was given. However, this difference is insufficient for a clear distinction because there is still a large mutual overlap of standard deviations between the RDAC values of the 3 groups, thus blurring an eventual threshold. Only an RDAC value lower than 0.58 minus the overlap of standard deviations from both sides (with vs. without reversal) resulting in a value of 0.2 would permit to assume a rocuronium dosing pattern that can be considered safe for the termination of anaesthesia without reversal (which obviously be confirmed using relaxometry). This value individually occurred in only one case from 60 of the non-reversal patients.

Conclusion

Finally, we can conclude from our results that the clinically applied neuromuscular relaxation patterns do not show a sufficiently clear difference in relation to the applied method of reversal or whether a reversal agent has been applied or not. In simple terms, we can summarise that it is impossible to estimate the need for the reversal of neuromuscular relaxation from the applied rocuronium dosing pattern. This inter-individual variation seen as an overlap of dosing patterns reflects the unpredictability of spontaneous recovery times of neuromuscular relaxants and underscores the necessity of objective monitoring.

Ethics Committee Approval: Ethics committee approval was received for this study from the Cantonal Ethical Committee (File No. 2016-01202), chaired by Peter Meier-Abt.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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